Major Kidney Clinical Research Studies and Projects Inventory*

Pirfenidone: Anti-Scarring Drug for Diabetic Nephropathy

1. Administrative Data

(a) Name of study/research project and acronym:

Pirfenidone: Anti-Scarring Drug for Diabetic Nephropathy

(b) Type of study/research project (randomized clinical trial, epidemiological study, database, etc.):

Randomized clinical trial

(c) Funding status (currently funded, study/project completed):

Currently funded.

(d) Recruitment status (recruitment completed, currently recruiting):

Currently recruiting

(e) For studies/projects currently recruiting, indicate total sample size/ number currently enrolled, anticipated period of recruitment:

Total sample size 120, enrollment start date is March 1, 2003, anticipated period of recruitment is 6-12 months.

(f) Data coordinating center principal investigator contact information (mailing address, phone, fax, and e-mail address):

Kumar Sharma, M.D.
Thomas Jefferson University
353 Jeff Hall
1020 Locust Street
Philadelphia, PA 19107
Phone: 215-503-6950
Fax: 215-923-7212
E-mail: kumar.Sharma@mail.tju.edu

(g) Number of recruiting sites, list of principal investigators at recruiting sites, and contact information:

Two recruiting sites: Thomas Jefferson University (Kumar Sharma) and NIH Intramural (Jeff Kopp)

(h) List of principal investigators at central laboratories/facilities (identify type of central facility) and contact information as in (f) and (g) above:

Kumar Sharma, M.D.
Thomas Jefferson University
353 Jeff Hall
1020 Locust Street
Philadelphia, PA 19107
Phone: 215-503-6950
Fax: 215-923-7212
E-mail: kumar.Sharma@mail.tju.edu

(i) Roster of Data and Safety Monitoring Board/Scientific Advisory Committee or other oversight committee(s):

Mary Leonard, M.D.; Peter Fumo, M.D.; Larry Weisberg, M.D.; Henry D'Silva, M.D.

(j) Private sector support (type of support, e.g., financial, donation of drugs/placebo, etc.)

Intermune, Inc., supplied the study drug.

2. Study Design (For completed studies- a copy of the primary publication can substitute for information below)

(a) Objective:

Evaluate efficacy of pirfenidone in patients with type1 and type 2 diabetes and advanced nephropathy.

(b) Study design:

Randomized, double blind, placebo-controlled, clinical trial with 120 type 1 and type 2 diabetic patients receiving either placebo or pirfenidone for a period of one year. Phase 2 clinical trial.

(c) Major inclusion criteria:

- Type 1or type 2 diabetics age ≥ 18 years

- Glomerular filtration rate between 25-75 ml/min/1.73m^2 calculated by the MDRD 4 variable formula
- A history of overt proteinuria (> 300 mg/24 hr or albumin positive by dipstick)
- A blood pressure controlled to ≤ 140/90 including treatment with ACR-I and/or ARB, if tolerated
- Willing not to become pregnant for the duration of the study

(d) Major exclusion criteria:

- Uncontrolled blood pressure
- Uncontrolled diabetes
- Hematologic disease
- Malignancy
- Liver disease
- Hepatitis B and C
- HIV +
- Other known renal disease besides diabetic nephropathy
- Taking immunosuppressive medication
- Class III or worse congestive heart failure
- A history of MI, unstable angina, CVA, TIA, or peptic ulcer within 6 months of study start
- A history of photosensitivity dermatitis
- Expectation of undergoing renal transplant or dialysis within 1 year of enrollment

(e) Description of the intervention(s):

Diabetic nephropathy is the leading cause of cases of kidney failure in the United States. In diabetic patients there is accumulation of proteins that lead to the formation of scar tissue and often, eventual progression to end-stage disease. A new investigational compound, pirfenidone, has been found to inhibit scarring and

matrix deposition in the kidney. Our hypothesis is that administration of pirfenidone to type 1 and type 2 diabetic patients with advanced diabetic nephropathy will lead to preservation of renal function.

(f) Baseline/eligibility visit schedule (number of visits, major assessments):

At the screening visit subjects will be informed about and consented to the trial. This visit includes a medical history, physical exam, blood and urine lab work, including TGF-β samples. If the subjects meet inclusion /exclusion criteria, they may return within two weeks for the baseline (randomization) visit. At that time, they will have a second set of lab work done and TGF-β samples obtained. Study drug or placebo will be dispensed at this time.

(g) Follow-up contact schedule (frequency, type of visit/phone, in-clinic, major assessments):

After the baseline visit, subjects will have 6 in-clinic visits and will be seen at weeks 2, 12, 24, 36, 52, and 54 weeks, which will conclude the trial period. Phone visits will occur at weeks 6, 18, 30, and 42 weeks.

(h) Primary outcome, secondary outcomes:

The primary endpoint will be the change in renal function from baseline to the end of the study. Renal function will be assessed by the 4 variable formula for GFR and factored for body surface area. The secondary endpoints, include the % change in urine albumin excretion from baseline to end of study period, the % change in levels of TGF-β1 in urine, plasma, and serum from baseline to end of study period and to determine the relationship between % change in TGF-β1 levels and the change in GFR.

(i) Brief summary of power estimates used to justify sample size/duration, including critical assumptions (i.e., effect-size estimates, estimated event rates, or rate of change in outcome measure):

We performed a statistical power analysis to determine the sample size necessary to have at least an 80% probability of detecting statistically significant differences and /or correlation for study endpoints. There will be an 81% power to detect, at a significance level or 0.05, a change of at least –0.230 ml/min/month (SD 0.40 ml/min/month) in GFR between 50 diabetic patients treated with pirfenidone and 50 diabetic patients treated with placebo. The estimates are based on the rate of decline in diabetic patients treated with ARBs, with the exception that the SD used in the power analysis was inflated because the sample size is smaller.

(j)Web site:

N/A at this time.

3. Data and Biological Sample Resources

(a) Biological samples collected in ongoing studies/research projects (specify the type of sample, e.g., blood, urine, etc., the amount, and the point in the study when samples were collected, e.g., baseline visit #1, baseline visit #2, follow-up visit #1; specify months after randomization/study entry)

N/A at this time.

(b) Biological samples currently in storage from completed trials (grid showing sample collection time, type of sample, amount, and number of study participants sample was collected from, and physical location of where the samples are stored):

N/A at this time.

(c) Brief summary of typical informed consent provisions (template informed consent form acceptable), including major variables in participant consents, if applicable (e.g., "use for other studies or not", "allow genetic studies or not."). Does consent include use of samples in other studies that are not part of the main study?

No genetic studies or use of samples for other purposes.

(d) Data collected (grid of data collection by time/clinic visit with specificity on the type of information collected, e.g., quality of life with SF-MOS 36, measurement of kidney function by GFR, serum creatinine measurement, etc.):

See Schedule of Assessment-Appendix A. GFR will be calculated by the MDRD 4 variable formula at visits screen, baseline, weeks 24, 52, and 54.

(e) Any provisions for distributing resources outside of the study? What is the sharing plan?

None

4. Ancillary Studies

(a) Process and contact person (name, address, phone, fax, and e mail address) for application to perform ancillary studies:

N/A

(b) List of ancillary studies approved, completed, and ongoing (including source of funding and amount):

N/A

5. List of Publications and Presentations (full citations, also note manuscripts in progress)

T. McGowan, S. Dunn, K. Sharma. Treatment of db/db mice with Pirfenidone leads to improved histology and serum creatinine. American Society of Nephrology. Toronto, Canada. October, 2000. (Manuscript in progress.)

***Cooperative Agreement, Contract, and Selected Investigator-Initiated, NIDDK-Supported Studies**

Appendix A. Pirfenidone Schedule of Assessments

	Screen	Baseline / Day 0	Week 2	Week 12	Week 24	Week 36	Week 52	Week 54/End of Treatmen Early Termination
Informed Consent	X							
clusion/Exclusion Criteria	X							
Medical History	X	X[a]						
Physical Exam	X	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X
Vital Signs	X	X	X	X	X	X	X	X
CMP	X			X	X	X	X	
Lipid Panel	X			X	X	X	X	
CBC (no diff)	X			X	X	X	X	
Hemoglobin A1-C	X			X	X	X	X	
Pregnancy Test	Serum	X[c]		X[c]	X[c]	X[c]	X[c]	X[c]
SMA-7		X						X
Urine Protein	X	X			X[d]		X[d]	X
Urinalysis	X	X		X	X		X	X
Urine TGF-Beta	X	X			X		X	X
GF-Beta levels in plasma	X	X			X		X	X
Dispense Study Drug		X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X
Collect Study Drug			X	X	X	X	X	X

[a] Interim medical history
[b] A targeted physical examination may be performed
[c] Urine pregnancy test